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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,070	10/30/2003	Frederic J. Kaye	221749	1623

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
05/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,070	KAYE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-26,35-43 and 45-54* is/are pending in the application.

4a) Of the above claim(s) *7,17 and 47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8-15,18-26,35-43,45 and 46* is/are rejected.

7)☒ Claim(s) *6 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection not reiterated in this Action is withdrawn.

Allowable Subject Matter

The indicated allowability of claims 40-43, 45 and 46 is withdrawn in view of the following new rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molecular and Cellular Biology 2002, vol. 22, pages 7688-7700) in view of Bass (Nature 2001, vol. 411, pages 428-429) and Bhanot (US 2004/0006005).

The claims are directed to compositions for inhibition of a gene that consist essentially of a fragment of the nucleotide encoding a Mect1-MAML2 chimeric gene and a nucleic acid complementary to the fragment wherein the fragment is 17-32 nucleotides in length. In specific embodiments the chimeric gene has the sequence shown in SEQ ID NO: 1 and results from a t(11;19) translocation. In other embodiments the composition is in a plasmid or viral vector that may comprise two different promoters such as RNA polymerase promoters, the fragment of the gene is of varying lengths and the composition contains 3' overhangs of 1-4 nucleotides that may be uridines.

Wu et al. teach the characterization of two genes that are mammalian homologue of the Mastermind gene of *Drosophila,* MAML2 and MAML3. The sequence of MAML2 is found in Genbank accession number XM_045716. Wu et al. teach that these genes are widely expressed in adult tissues but exhibit distinct expression patterns in mouse early spinal cord development, indicating that MAML proteins may modify Notch signaling in different cell types and contribute to the diversity of biological effects that result from Notch activation based on their own expression levels and differential activities (see abstract). Wu et al. do not teach siRNAs targeted to MAML2.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. Bass further teaches in the same column that the discovery of short interfering RNAs that are functional in mammalian cells will inspire further research studies aimed at optimizing the use of siRNAs, as well as at understanding why conventional RNAi using longer dsRNA works in eggs and embryos. Bass speculates that, based on the huge impact the RNAi technique has had in studies of non-mammalian systems, use of siRNA in mammalian cells could be just as far-reaching, with applications extending to functional genomics and therapeutics.

Bhanot teaches at paragraph 12 that preferred target regions for expression inhibitors such as siRNAs include the coding region and the stop codon region, defined in paragraph 31 as a portion of a gene encompassing from about 25 to about 50 contiguous nucleotides in either direction from a translation termination codon. Bhanot incorporates by reference at paragraph 27 the teachings of other artisans regarding siRNA and vector design including teaching that vectors can be plasmids or viral vectors (found in WO 01/36646), vectors can comprise two RNA strands under control of different RNA polymerase promoters (found in WO 99/32619) and that siRNAs can comprise 3' overhangs that comprise uridine (found in Elbashir et al, EMBO Journal).

Based on this, Bhanot teaches that design of a siRNA or a vector coding for the siRNA to inhibit a nucleotide sequence is well within the skill of the ordinary artisan.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to target MAML2 with siRNAs for the purpose of studying gene function as taught by Bass and to make the siRNA targeted to the stop codon region as taught by Bhanot. Wu et al. provide a motivation to target MAML2 in order to study its function by teaching that MAML2 is involved in Notch signaling and contributes to the diverse biological effects that result from Notch activation. Bass provides a motivation to make siRNAs to a gene of interest by teaching they are more effective than antisense oligonucleotides and that the use of siRNAs is poised to have a huge impact on studies of mammalian systems such as study of gene function. Bhanot provides a motivation to make a siRNA targeted to the stop codon region of MAML2 by teaching that it is a preferred target region for inhibitory nucleic acids. One of ordinary skill in the art would have had a reasonable expectation of success in making siRNAs to MAML2 because the sequence of MAML2 is known and Bhanot teaches that design of siRNAs to target a gene is readily accomplished by those in the art. Because the chimeric gene that encodes SEQ ID NO: 12 comprises MAML2 and in particular comprises the stop codon region of this gene, any siRNA targeted to this region of MAML2 will necessarily comprise a fragment of a nucleic acid encoding SEQ ID NO: 12 and a nucleic acid complementary to this fragment and will, absent evidence to the contrary, inhibit the translation of a MECT1-MAML2 gene.

Thus, the invention of claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 4, 5, 8-13, 18-26, 36, 38-41, 43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 above, and further in view of Nicklin et al. (Current Gene Therapy 2002, of record) and Sui et al. (PNAS 2002, of record).

Claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 are described in the previous rejection over Wu et al., Bass and Bhanot. Claim 11 recites a viral vector that is an adenoviral vector. Claim 22 recites RNA polymerase III (Pol III) promoters.

The teachings of Wu et al., Bass and Bhanot are described in the previous 103 rejection. Wu et al., Bass and Bhanot do not teach compositions in an adenoviral vector or use of Pol III promoters.

Nicklin et al. teach that replication defective adenoviral vectors have been successfully used for gene delivery in many applications.

Sui et al. teach DNA vectors for producing siRNA molecules suitable for use in RNA interference. These vectors are plasmids that operate under control of the U6 promoter, which is a Pol III promoter.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described in the previous 103 rejection. It would have been further obvious to use an

adenoviral vector or a vector that comprises a Pol III promoter. Sui et al. provide a motivation and reasonable expectation of success in using vectors comprising Pol III promoters by teaching their successful use to produce siRNAs that reduce gene expression. Nicklin et al. provide a motivation and expectation of success in using an adenoviral vector by teaching that adenoviral vectors are widely used as gene delivery systems.

Thus, the invention of claims 1, 4, 5, 8-13, 18-26, 36, 38-41, 43, 45 and 46 would have been obvious, as a whole, at the time of invention.

Claims 1, 4, 5, 8-10, 12, 13, 15, 18-21, 23-26, 36-41, 43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 above, and further in view of Parrish et al. (Molecular Cell 2000, of record)

Claim 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 are described in the 103 rejection under Wu et al., Bass and Bhanot. Claims 15 and 37 recite the complementary nucleic acid can contain up to 3 base substitutions.

The teachings of Wu et al., Bass and Bhanot are described in the 103 rejection over these references. They do not teach siRNAs comprising base substitutions, but Parrish et al. teach that base substitutions commonly used in nucleic acid therapeutics are tolerated in the double stranded RNAs used for RNA interference.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described above. It would have been further obvious to one of ordinary skill in the art at

the time of invention to make siRNAs containing base substitutions. Parrish provides a motivation and reasonable expectation of success in using base substitutions, teaching that base modifications known in the art of nucleic acid therapeutics to impart increased stability are tolerated in the double stranded RNA used in RNA interference.

Thus, the invention of claims 1, 4, 5, 8-10, 12, 13, 15, 18-21, 23-26, 36-41, 43, 45 and 46 would have been obvious, as a whole, at the time of invention.

Claims 1, 3-5, 8-10, 12-14 18-21, 23-26, 35, 36, 38-43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al., Bass and Bhanot as applied to claims 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 above, and further in view of Beach et al. (US 2004/0086884) and Taylor et al. (US 6,331,425).

Claim 1, 4, 5, 8-10, 12, 13, 18-21, 23-26, 36, 38-41, 43, 45 and 46 are described in the 103 rejection under Wu et al., Bass and Bhanot. Claims 3, 14, 35 and 42 recite the presence of a sequence recognized by a restriction enzyme that may be Hin dIII that joins the sequences of the composition.

The teachings of Wu et al., Bass and Bhanot are described in the 103 rejection over these references. They do not teach siRNAs comprising a hairpin loop that contains a restriction enzyme site, but Taylor et al. teach Hin dIII is one example of a restriction enzyme at column 3, first paragraph and Beach et al. specifically teach siRNA hairpin loops containing restriction sites in claim 53.

The teachings of Wu et al., Bass and Bhanot are obvious for the reasons described above. It would have been further obvious to one of ordinary skill in the art at

the time of invention to incorporate a restriction site into a hairpin loop. Beach et al. provide a motivation and reasonable expectation of success by explicitly teaching siRNAs comprising such loops. Given the knowledge in the art that Hin dIII is a restriction enzyme as evidenced by Taylor et al., one of ordinary skill in the art would recognize the use of that particular enzyme to be mere design choice.

Thus, the invention of claims 1, 3-5, 8-10, 12-14 18-21, 23-26, 35, 36, 38-43, 45 and 46 would have been obvious, as a whole, at the time of invention.

Allowable Subject Matter

Claims 6 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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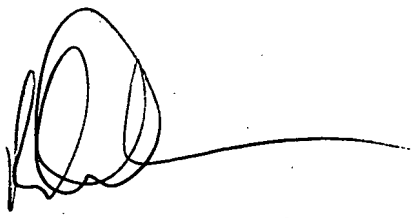
Tracy Vivlemore
Examiner
Art Unit 1635

TV
May 22, 2007



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